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Pharmacy Compounding Advisory Committee: FDA Immunogenicity Risk of Compounded Peptides October 29, 2024

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Disclosure

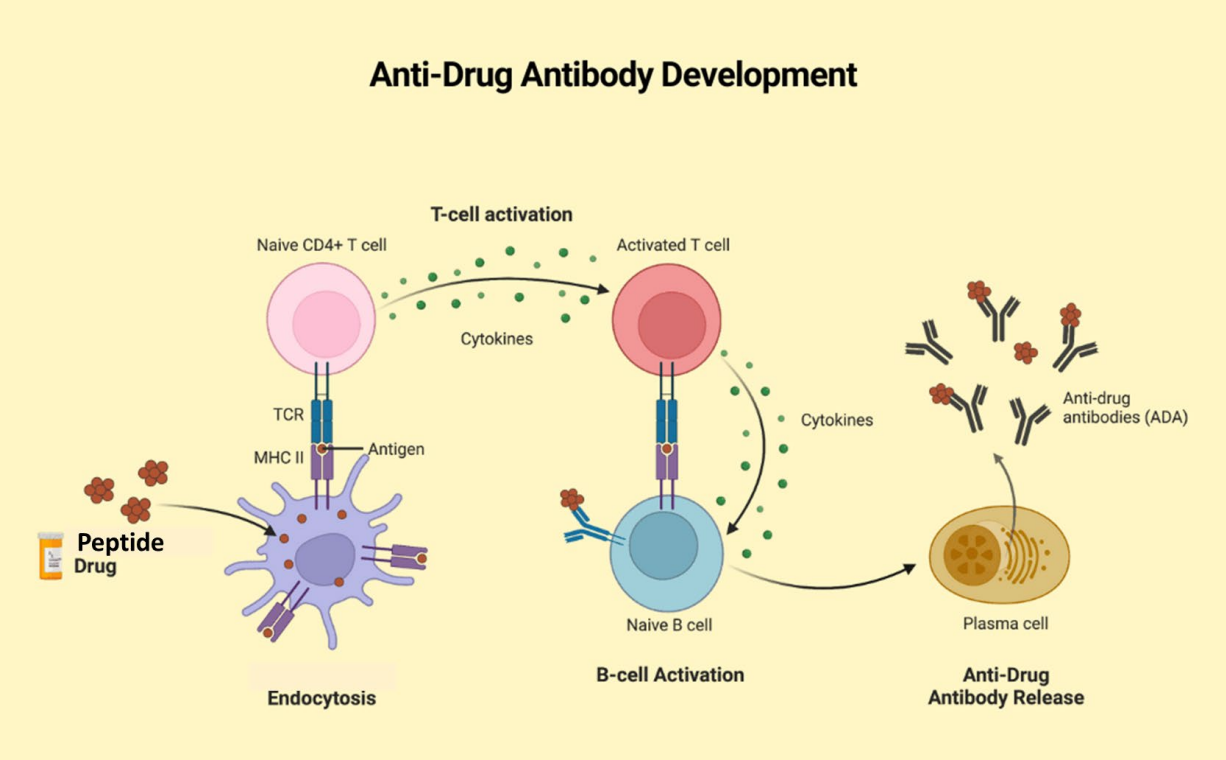
- **This speaker has no conflicts of interest to disclose**

Talk Map:

- **Product immunogenicity**
- **Describe the clinical immunogenicity concerns for peptides**
- **Brief introduction to the mechanisms involved in generating an immune response to a product**
- **Discuss the immunogenicity–related concerns for compounded complex peptide products**

Immunogenicity Concerns for Peptide Products

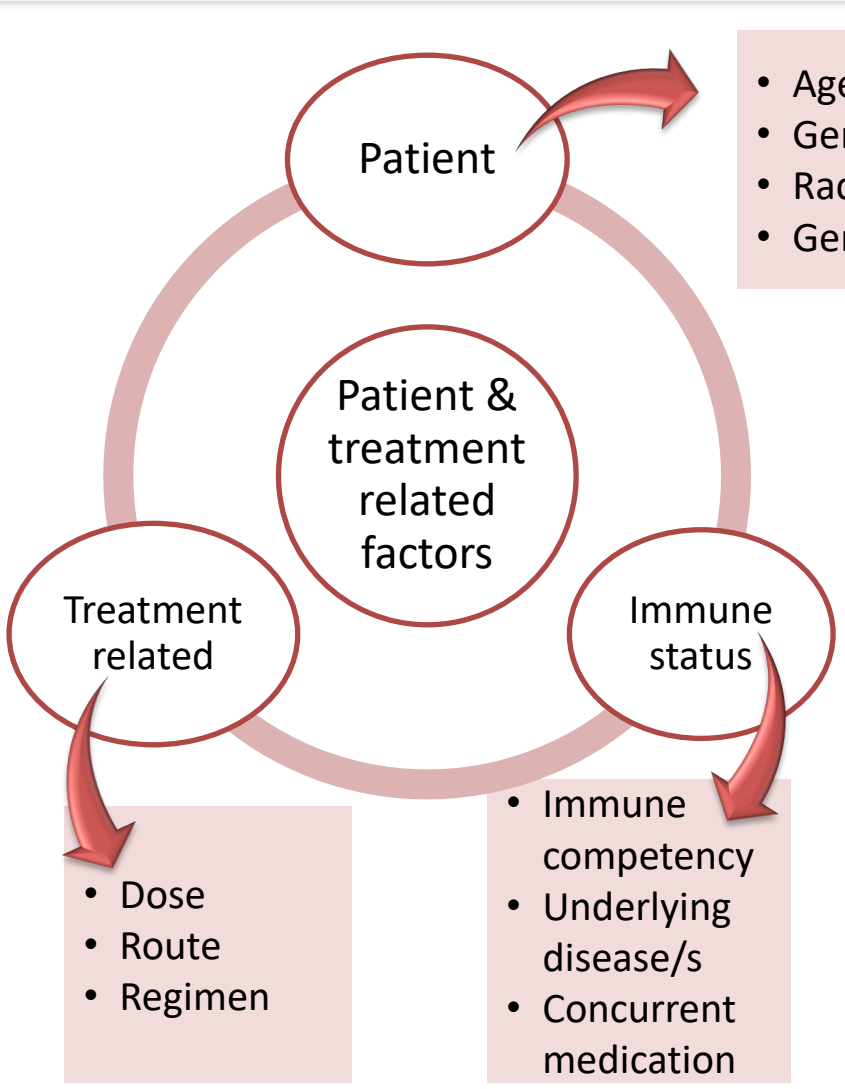
- Immunogenicity is the unwanted development of an immune response, usually antibodies, elicited by a therapeutic product.
- Therapeutic peptides can induce an unwanted antigen(Ag)-specific immune response that can impact on safety and/or efficacy

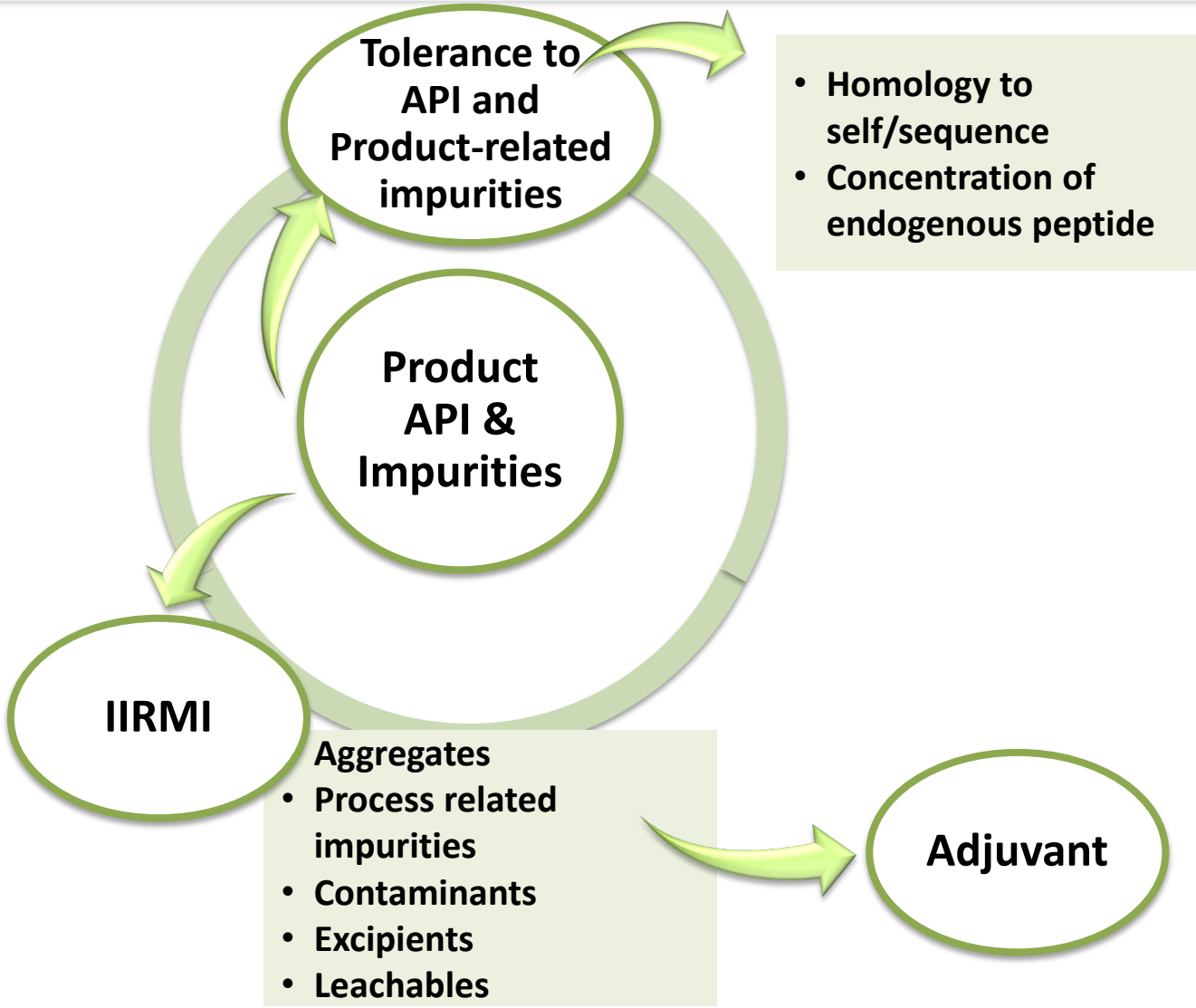


Clinical Immunogenicity Concerns for Peptide Products

- None
  - No apparent effects
- Moderate
  - Alterations in pharmacokinetic/pharmacodynamic (PK/PD) leading to loss of efficacy or toxicity
- Severe
  - Hypersensitivity/Anaphylaxis (IgG or IgE)
  - Immune complex disease (IgG)
  - Neutralizing antibody, precludes efficacy of effective therapy
  - Cross-reactive neutralization of unique endogenous counterpart

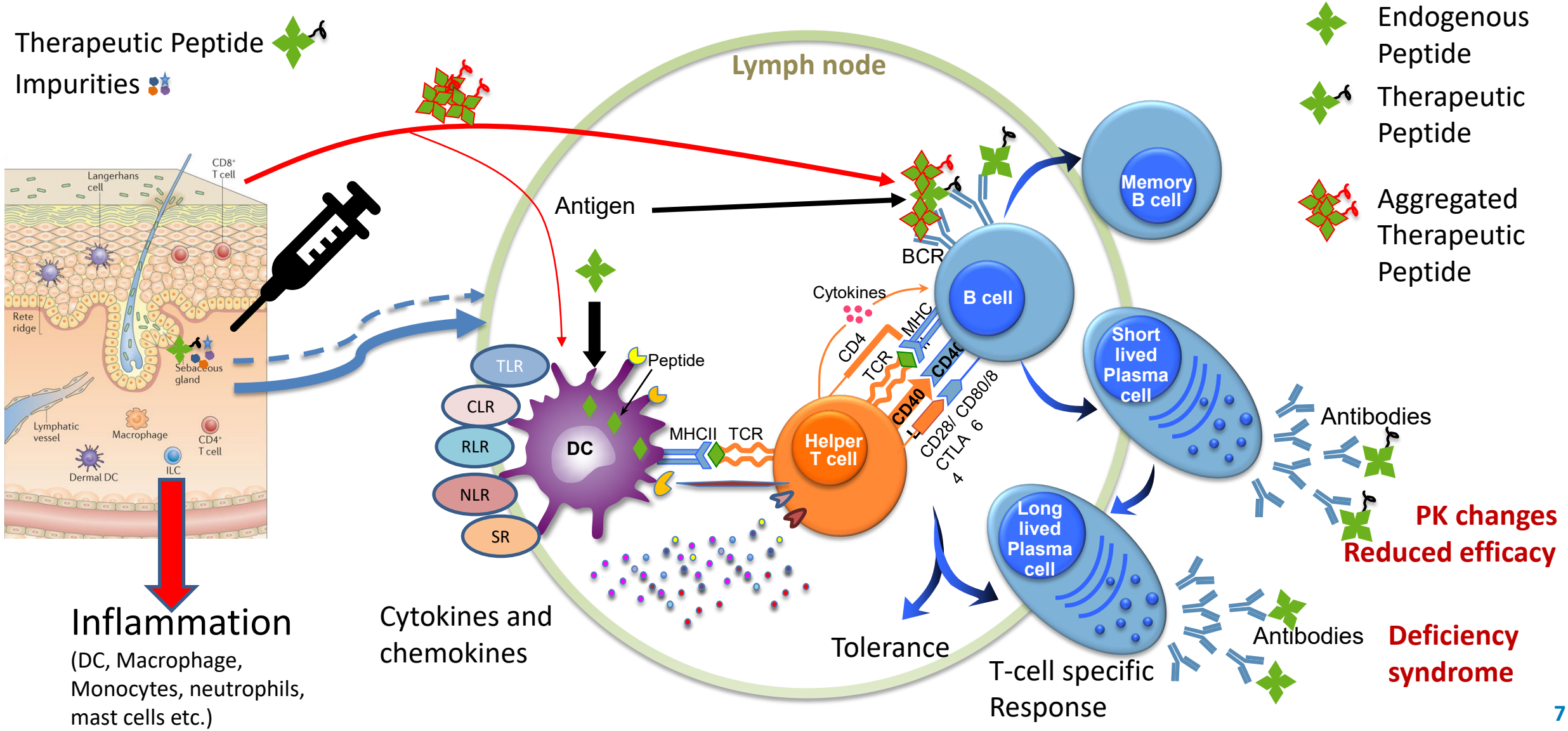
Immunogenicity Risk Factors:



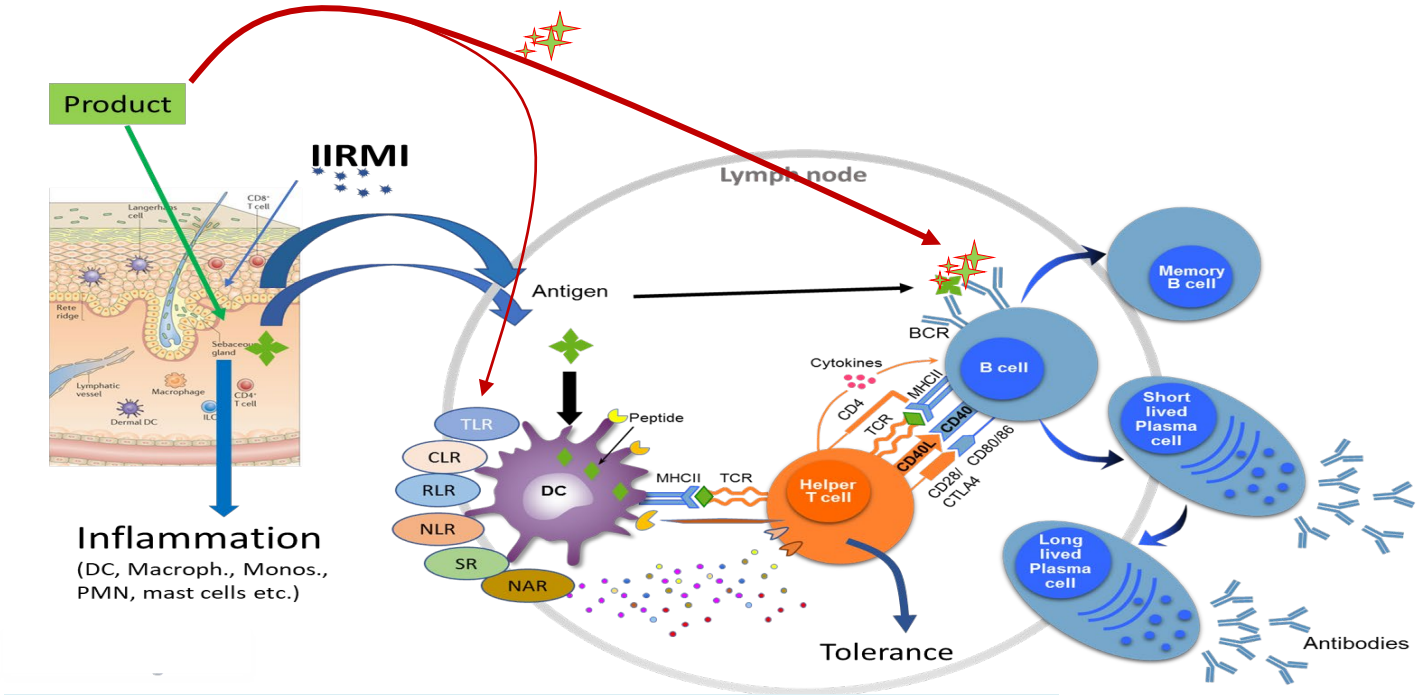


Abbreviations: API = active pharmaceutical ingredient, IIRMI = innate immune response modulating impurities, MHC = major histocompatibility complex

Impurities can increase the immunogenicity risk of peptides



Product and process related impurities impact on the immunogenicity risk for peptides



For most peptides capable of inducing an immune response, impurities can change the **quantity** and the **quality of the immune response**

Aggregation profile

Visible and subvisible particles

Process - related impurities	Innate immune activation by IIRMI In vitro (IIRMI, Ag uptake, DC maturation)
Product – related impurities	LC-MS, MS-MS, Peptide mapping, etc. Methods that assess binding to MHC In silico In vitro (MHC binding, MAPPs) Methods that assess T cell activation In vitro (DC-T cell)

Immunogenicity risk of peptides

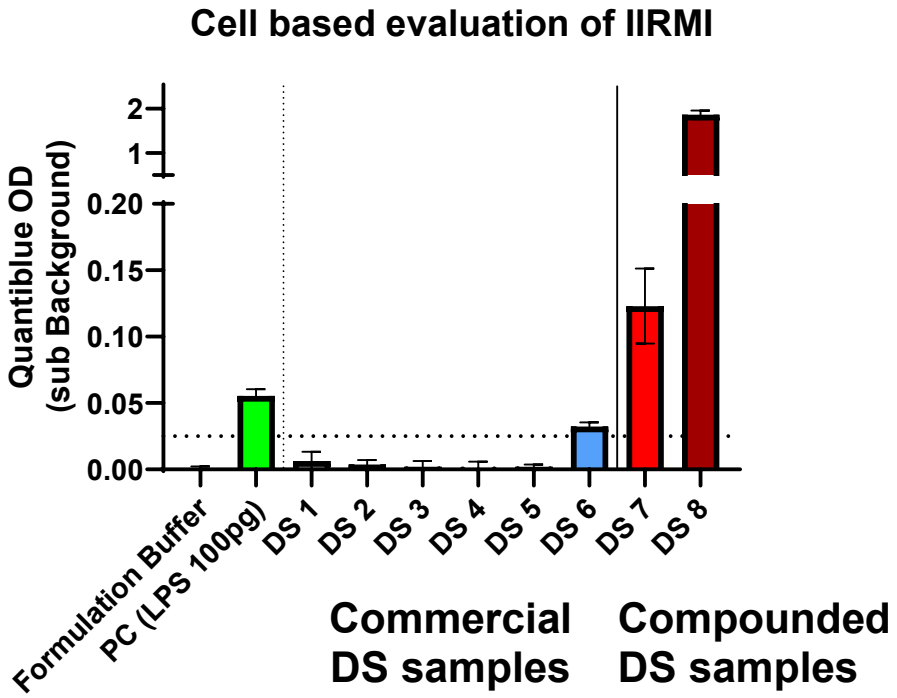
- **Level of concern with peptides is different than for small molecule: Peptide sequences can elicit an immune response, particularly if aggregated or presented on scaffolding.**
- **Peptides administered via subcutaneous, intravenous, intramuscular, intradermal, inhalation, and intravitreal routes have greater immunogenic risk than oral or transrectal peptides.**
- **Product formulation is critical to the quality and stability of peptide drug products. Formulation differences can modify peptide stability and immunogenicity.**
- **Peptide-related impurities may modify the target of the antibodies developed.**
- **Impurities or contaminants that activate immune cells may increase the immunogenicity of the API or result in immune responses that target new sequences that may cross-react with endogenous counterparts.**

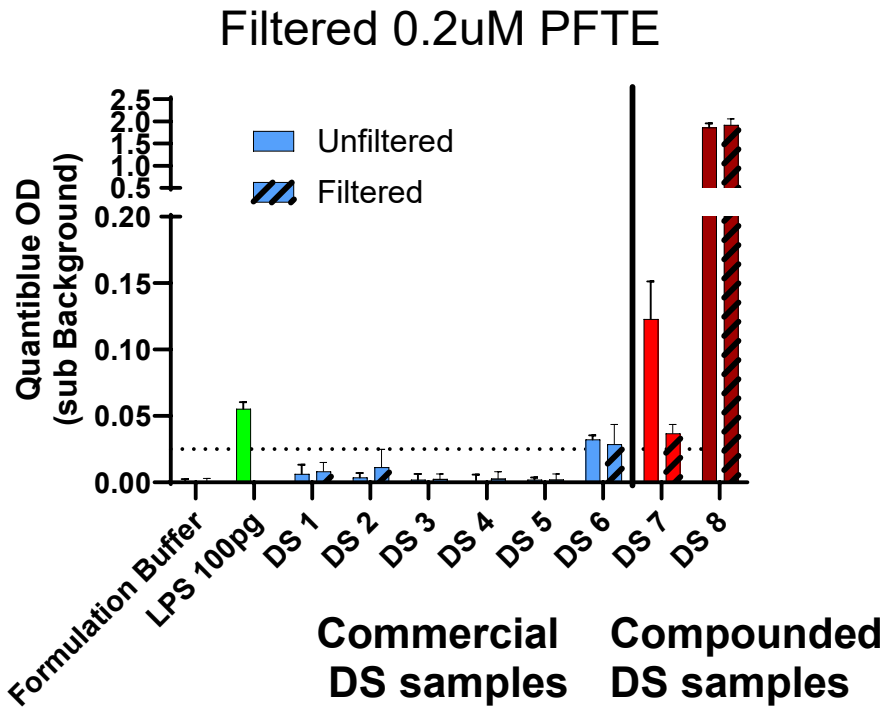
Immunogenicity risk of impurities in peptides

- **Peptide-related impurities can be difficult to detect, analyze, and control because the impurities can have similar amino acid sequences to the peptide itself, necessitating advanced analytical techniques, such as liquid chromatography-high resolution mass spectrometry, to detect, identify, and quantify impurities.**
- **Impurities and contaminants can activate the immune cells where the product is deposited increasing the immunogenicity risk at trace levels (pg-ng).**
- **Assessing the immunogenicity risk of the immunomodulatory impurities in peptides requires complex in silico and in vitro studies.**
- **Mitigating the immunogenicity risk of peptides requires sensitive assays and control of product and process impurities.**

Immunogenicity risk of peptides

- **The risk of Innate Immune Response Modulating Impurities may or may not be mitigated by the drug product (DP) manufacturing process.**





Abbreviations: DS = drug substance, LPS = lipopolysaccharide, PC = phosphorylcholine, PFTE = polytetrafluoroethylene

Summary

- **Product immunogenicity constitutes a risk for peptides, including compounded peptides, especially when delivered via certain routes of administration, which may result in significant risks of harm, including life-threatening reactions such as anaphylaxis. Control of impurities, including aggregates, can mitigate this risk but requires sophisticated manufacturing and testing strategies.**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Pharmacy Compounding Advisory Committee: Bulk Drug Substance (BDS) Discussion October 29, 2024

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Disclosure

- **This speaker has no conflicts of interest to disclose**

Rationale and Objectives

- **In at least one evaluation to be presented today, we explain that despite the lack of clarity about which BDS the nominator intended to propose, due to FDA's significant safety concerns related to the use of the substance in compounding drug products, FDA has decided to evaluate these multiple related BDSs on its own initiative.**

- **Goals of this presentation:**

  - **Explain regulatory definitions for BDS, active pharmaceutical ingredient (API), and active moiety (AM)**

  - **Explain how BDS differences have implications for the drug products made with them**

  - **Provide other relevant background**

A Thought Experiment…

- **How many BDS, API, and AM in the example below?**

- Diclofenac - Diclofenac Epolamine - Diclofenac Sodium - Diclofenac Potassium	- Naproxen - Naproxen Sodium

Statute and Regulations

- **Per 21 CFR 207.3, a BDS is the same as an Active Pharmaceutical Ingredient (API). Section 207.3 reads "*Bulk drug substance*, as referenced in sections 503A(b)(1)(A) and 503B(a)(2) of the Federal Food, Drug, and Cosmetic Act, previously defined in § 207.3(a)(4), means the same as "active pharmaceutical ingredient" as defined in § 207.1."**

- **API is defined in FDA regulations at 21 CFR 207.1 as "any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance."**

BDS/API In Practical Terms

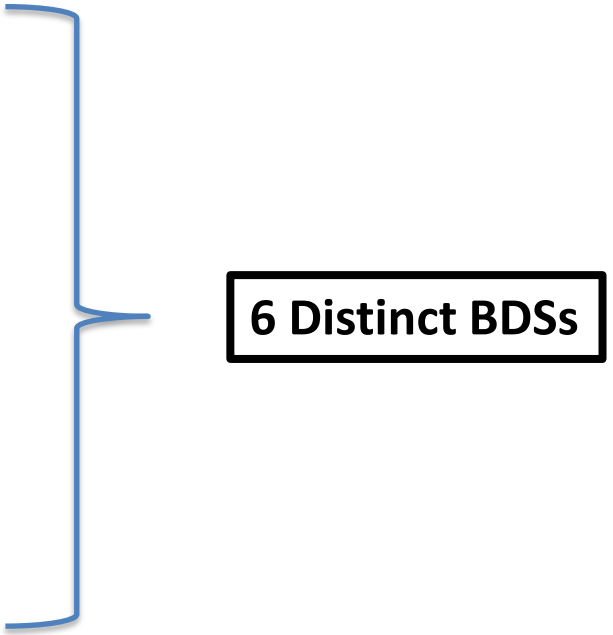
- **The specific "form" of API used in a formulated product is often a salt or an ester of a free base or active moiety; each a distinct API/BDS**
- **That "form" is chosen for its physical, chemical, or pharmacokinetic-pharmacodynamic (PKPD) characteristics which renders them more suitable for drug product processing**
- **The selection can be dosage form specific due to unique Critical Quality Attributes (CQA) associated with a desired dosage form**

What is an Active Moiety and Salt Form?

- An active moiety is defined at 21 CFR 314.3 as “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.”

- Diclofenac – Free base and active moiety non-steroidal anti-inflammatory drugs (NSAID)
- Diclofenac Epolamine – Epolamine salt of diclofenac free base
- Diclofenac Sodium – Sodium salt of diclofenac free base
- Diclofenac Potassium – Potassium salt of diclofenac free base

- Naproxen – Free base and active moiety NSAID
- Naproxen Sodium – Sodium salt of naproxen free base



Why Does This Matter?

- **With respect to compounding under section 503A, FDA has stated that "when a salt or ester of an active moiety is listed [on the 503A bulks list], only that particular salt or ester may be used. The base compound and other salts or esters of the same active moiety must be evaluated separately for eligibility."**
  - **See 2016 proposed rule: https://www.federalregister.gov/d/2016-30109/p-108**
  - **This rule was finalized in 2019.**

Why Does This Matter?

- Different API "forms" such as salts, esters and the free base can have very different properties
  - Physicochemical properties
    - Chemical formula/Molecular weight
    - Solid state stability
    - Solution stability
    - Solubility
    - Polymorphism
  - Pharmacology/toxicology profile
  - PK/PD profile

- These distinctions are as important in compounding as they are in conventional drug product manufacturing. This is not just important from a regulatory perspective but also as a critical matter for patients as these different forms have different chemical structures as well as different physical, chemical, PK/PD characteristics. This can impact product safety and efficacy.

Unique Identifiers and Related Databases

- Global Substance Registration System (GSRS)
  - Used by multiple worldwide regulatory agencies
  - Home of a Unique Ingredient Identifier (UNII)

- Chemical Abstracts Services (CAS)
  - Home of unique identifier known as CAS Registry Number (CAS RN)

- Databases generally “populated” by manufacturers/suppliers
  - They provide structure and related information and request unique identifier
  - Regulators do not own or police the data contained therein

- Use of “common names” for nominated substance can be highly problematic and cause widespread confusion

Physical and Chemical Characterization

- **[For] physical and chemical characterization of the substance, FDA would consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified consistently based on its physical and chemical characteristics. If a substance cannot be well characterized chemically and physically, the Agency proposes that this *criterion weigh against its inclusion […] because there can be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the Agency*." *Emphasis added*.**
  - **2016 Proposed Rule, Docket No. FDA-2016-N-3464.**
  - **See 81 FR 91071**
- **FDA considers these factors in the context of each specific BDS, which has unique characteristics and risks.**
  - **For example, we identify peptide-related impurities as a risk related to peptides**
- **Botanical BDS are complex mixtures, and care must be taken to identify a single BDS**

Conclusion

- **BDS is defined as the same as an API in the regulations. A free base form as well as each of the salt forms are each distinct BDS, each with unique physical, chemical and PK/PD characteristics which can impact product safety and efficacy**

- **Nominators, BDS Manufacturers, and Compounders need to be aware of what single BDS is nominated, manufactured, and used to formulate a compounded product**

- **UNII and CAS# are unique identifiers for API/BDSs but not controlled by FDA**

- **Our physical and chemical characterization evaluation and conclusion is specific to each unique BDS**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Ipamorelin-related Bulk Drug Substances

Pharmacy Compounding Advisory Committee Meeting

October 29, 2024

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Special Thanks to:

Office of New Drugs- Division of Gastroenterology, Division of General Endocrinology

Nomination

- Ipamorelin (free base) and ipamorelin acetate were nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
- Two nominations
  - Wells Pharmacy Network (Document ID: FDA-2015-N-3534-0283) nominated ipamorelin acetate
  - LDT Health Solutions (Document ID: FDA-2018-N-2973-0002) nominated ipamorelin (free base)
- Nominators withdrew nominations
  - Wells Pharmacy Network on 9/19/24 (Document ID: FDA-2015-N-3534-0471)
  - LDT Health Solutions on 9/19/24 (Document ID: FDA-2015-N-3534-0472)
- However, FDA is electing to proceed with the presentation of this evaluation to PCAC
- Evaluated for:
  - Growth hormone deficiency (GHD) and postoperative ileus (POI)
- Proposed dosage form is subcutaneous (SC) injection in 2000 mcg/mL

Evaluation Criteria

- Physical and chemical characterization
- Historical use in compounding
- Available evidence of effectiveness or lack of effectiveness
- Nonclinical and clinical safety

Summary of Basic Information on Ipamorelin Free Base and Ipamorelin Acetate

	Ipamorelin (free base)	Ipamorelin Acetate
UNII Code	Y9M3S784Z6	Not available
CAS No	170851-70-4	1258196-85-8
Molecular Formula/ Molecular Weight (MF/MW; g/mol)	$C_{38}H_{49}N_9O_5$/711.9	$C_{38}H_{49}N_9O_5.xCH_3COOH$/NA
Chemical Structure	H-Aib-His-D-2Nal-D-Phe-Lys-NH_2	H-Aib-His-D-2Nal-D-Phe-Lys-NH_2 x·CH_3COOH
Supplier Availability	Yes	Yes
Active Moiety	Ipamorelin (free base)	Ipamorelin (free base)

Summary of Information Submitted in Two Nominations

Nominator	Wells Pharmacy Network	LDT Health Solutions
Nominated BDS	Ipamorelin Acetate	Ipamorelin
BDS per UNII code	Y9M3S784Z6 (*matches Ipamorelin free base*)	Y9M3S784Z6 (*matches Ipamorelin free base*)
CoA	CoA provided for Ipamorelin Acetate	CoA provided for Ipamorelin Acetate
CAS No.	170851-70-4 (*matches Ipamorelin free base*)	170851-70-4 (*matches Ipamorelin free base*)
MF	$C_{38}H_{49}N_9O_5$ (provided in the CoA) (*matches Ipamorelin free base*)	$C_{38}H_{49}N_9O_5$ (provided in the CoA) (*matches Ipamorelin free base*)
MW (g/mol)	711.9 (provided in the CoA) (*matches Ipamorelin free base*)	711.9 (provided in the CoA) (*matches Ipamorelin free base*)
Chemical Name	Aib-His-D-2-Nal-D-Phe-Lys-NH_2 (*matches Ipamorelin free base*)	Aib-His-D-2-Nal-D-Phe-Lys-NH_2 (*matches Ipamorelin free base*)
Active Moiety in Clinical References	Ipamorelin Free Base	Ipamorelin Free Base

Italics in the table above represents FDA assessment.

Physical and Chemical Characterization (1)

Ipamorelin Acetate

- Acetate salt of the pentapeptide ipamorelin
- White to off-white lyophilized powder; soluble in water at 20 mg/mL
- Has no USP drug substance monograph
- Stability
  - Manufacturers recommend storage in a sealed container at 2°C to 8 °C in a fridge or freezer
  - Remain stable up to 4 years when stored at - 20 °C
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation
- Impurities
  - Peptide-related impurities and peptide synthesis process-related impurities (e.g. starting materials, residual solvents, coupling reagents, activators, catalysts)

Physical and Chemical Characterization (2)

- Potential for immunogenicity
  - CoA includes identification, assay, water content and acetate content but no testing result for the control on impurities, aggregates and bioburden/endotoxin levels
  - Literature search showed single impurity less than 2% in CoA, however, there is no information regarding the nature of individual impurities that can be present at up to 2.0% level

Conclusion: ipamorelin acetate is not well-characterized

- Lack of certain critical characterization data (impurities, aggregates, and bacterial endotoxin levels)
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities
- Unnatural AAs may add to the complexity of characterization of ipamorelin acetate

Physical and Chemical Characterization (3)

Ipamorelin (Free Base)

- Pentapeptide (Aib-His-D-2Nal-D-Phe-Lys-NH_2) reported to be a ghrelin mimetic with growth hormone (GH) releasing activity:
  - containing non-proteinogenic amino acids (AA), including Aib (Aminoisobutyric acid) and Nal (naphthylalanine)
  - May add to the complexity of the characterization of ipamorelin (free base)
- White lyophilized powder; limited solubility in water (slightly soluble in water at 0.0032 mg/mL)
- Has no USP drug substance monograph
- Stability
  - Manufacturer recommends storing desiccated below -18 °C ; upon reconstitution, ipamorelin (free base) in solution is stable for 2-3 weeks stored at 4°C and for 3-4 months at -20°C
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (4)

- Potential for Impurities
  - Peptide-related impurities and peptide synthesis process-related impurities (e.g. starting materials, residual solvents, coupling reagents, activators, catalysts)
- Potential for immunogenicity
  - No Certificate of Analysis (CoA) (for free base) in the nomination
  - No information on impurity limits/testing results as critical attribute control in the CoA reported
  - Lack of information on the potential of peptide aggregation, especially when formulated in an injectable dosage form for SC administration

Conclusion: ipamorelin (free base) is not well-characterized

- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities.
- Limited water solubility makes it difficult to formulate proposed injectable dosage form at the concentration of 2 mg/mL using water as a solvent.
- Unnatural AAs may add to the complexity of characterization of ipamorelin (free base)

Historical Use in Compounding (1)

Ipamorelin-related bulk drug substances:

- First identified in 1998 (Raun et al. 1998)
- Although ipamorelin has been used in the past, there is insufficient information available to determine how long it has been used in compounding
- Based on outsourcing facility (OF) reporting data, compounding with ipamorelin can be traced back to at least 2017
- Uses
  - POI following abdominal surgery
  - Growth hormone deficiencies

Historical Use in Compounding (2)

- Have been used extensively in medical spas and wellness clinics
  - Unclear if compounded ipamorelin has been used, however one medical clinic reports “partnering with FDA-regulated compounding pharmacies”
- Are marketed online:
  - For weight loss management, anti-aging, sleep cycle improvement, and bodybuilding
  - In combination with other peptides such as sermorelin acetate and CJC-1295
  - In injectable, oral, and nasal formulations
- Have been used in sports as a doping agent
- Not recognized in the National Medical Registries, European Medicines Agency website, European, Chinese, Indian, or Japanese Pharmacopoeias

Historical Use in Compounding (3)

- **Conclusion**: There is some evidence of compounded ipamorelin's use in humans. Internet search results show that compounders have been preparing ipamorelin in injectable, nasal, and oral formulations marketed for a variety of uses. These formulations of ipamorelin are increasingly being marketed by medical spas and wellness clinics

General Pharmacology

- Ipamorelin acts as an agonist of ghrelin receptors (ghrelin mimetic)
- GH release
  - Ipamorelin stimulates GH release from anterior pituitary via activation of ghrelin receptors in growth hormone releasing hormone (GHRH)-positive neurons in hypothalamus (Hansen et al. 2001; Raun et al. 1998)
- Gastrointestinal motility
  - Ipamorelin stimulates both gastric acid secretion and gastric motility via ghrelin receptor activation in the stomach (Masuda et al. 2000)

Pharmacokinetics (1)

Nonclinical pharmacokinetic (PK) information for ipamorelin-related substances:

- Nonclinical studies assessing the PK and toxicological profile of ipamorelin-related substances delivered via SC route of administration were not identified
- In rats, ipamorelin acetate (1 mg/kg, IV) had a short half-life (27 min), was resistant to metabolism, and was excreted in urine (Johansen et al. 1998)

Pharmacokinetics (2)

Clinical pharmacokinetic (PK) information for ipamorelin-related substances:

- Gobburu et al. 1999:
  - R, PC, dose-escalation, PK and PD study in 48 healthy adult male subjects
    - 5 groups of 6 healthy male subjects per group received ipamorelin from 4.21 to 140.45 nmol/kg over a 15-minute IV infusion
    - 2 subjects per group received placebo
  - Results
    - Linear PK: ipamorelin has short half-life of 2 hours, systemic clearance of 0.078 L/h/kg and steady-state volume of distribution of 0.22 L/kg
    - Linear PD of GH release: maximum plasma GH concentration is 465 mIU/L. All concentrations declined to very low concentration at all doses by 6 hours

Overview of Growth hormone deficiency (GHD)

- GHD:
  - Characterized by inadequate secretion of GH from pituitary gland
  - Can be congenital or acquired
    - Some cases have no known or diagnosable cause (idiopathic) and may be childhood- or adult-onset
  - Can be complete (inability secrete GH) or partial
- Diagnosis: signs and symptoms and GH stimulation tests using provocative agents
  - Random GH level is not useful because levels fluctuate throughout day
  - Insulin-like growth factor 1 (IGF-1) levels are helpful in screening
- Signs and symptoms may include:
  - Childhood: low blood glucose levels in infants and toddlers, growth failure, short stature, and maturation delays
  - Adulthood: reduced energy levels, altered body composition, osteoporosis, reduced muscle strength, lipid abnormalities, insulin resistance, and impaired cardiac function

Treatment of GDH

- Multiple recombinant human GH (rhGH) preparations approved for children with growth failure due to inadequate secretion of endogenous GH and adults with GHD
- In pediatric patients with GHD:
  - GH is used to normalize annual growth velocity and final adult height
  - Doses are titrated based on growth response. IGF-1 levels monitor adherence and safety
- In adults with GHD:
  - GH offers benefits in body composition, exercise capacity, and quality of life (Molitch et al. 2011)
  - GH dose is titrated according to clinical response, side effects, and IGF-1 levels

Clinical Effectiveness – GHD

- FDA has not identified data to support effectiveness of ipamorelin-related substances for the diagnosis or treatment of GHD in children or adults
  - Although a study in healthy subjects administered single doses of IV ipamorelin showed increased GH levels, there are no effectiveness studies in subjects with GHD
  - No data on whether ipamorelin will increase GH levels in subjects with partial or complete GHD
    - Partial GHD: patients may lose responsiveness over time due to depletion of GH stores
    - Complete GHD: patients would not likely improve in response to GHS stimulation
- There are currently FDA-approved therapies with established efficacy for GHD

Overview of Postoperative Ileus (POI)

- POI is defined as transient cessation of coordinated bowel motility after surgical intervention which prevents effective transit of intestinal contents or tolerance of oral intake
- POI is associated with significant postoperative morbidity, reduced patient satisfaction and prolonged hospitalization
- Risk factors
  - Opioid use, paralytic enteric nervous system reflexes, inflammation following surgery
- Clinical signs and symptoms
  - Abdominal distention, bloating, nausea, vomiting, abdominal pain, reduction of bowel sounds, inability to tolerate solid food, delayed passage or inability to pass flatus or stool

Treatment of POI

- Objectives: accelerating GI recovery and decreasing hospital length of stay
  - Non-pharmacological treatment
    - Early reintroduction of nutrition, gum chewing, laparoscopic surgery, epidural anesthesia, limited excess fluid
  - Pharmacological treatment
    - Alvimopan is the only FDA-approved drug for accelerating time to upper and lower GI recovery following bowel resection
    - Symptomatic management
      - Methylnaltrexone, metoclopramide, neostigmine, celecoxib

Clinical Effectiveness – POI (1)

- There are no clinical studies for the treatment of POI via proposed SC route of administration
- Beck et al. 2014:
  - Proof-of-concept, phase 2, MC, R, DB , PC trial to evaluate upper GI recovery in 117 hospitalized adults following abdominal surgery (laparotomy or laparoscopic)
    - IV Ipamorelin 0.03 mg/kg (n=56) or placebo (n=58) twice daily started on postoperative day (POD) 1 until POD 7 or hospital discharge, whichever occurred first

Clinical Effectiveness – POI (2)

- Primary endpoint
  - Time from first dose of study drug to first tolerated meal without nausea or vomiting (recovery of upper GI tract)
- Secondary endpoints
  - Time to first bowel movement (recovery of lower GI tract)
  - Time when patient is ready for hospital discharge based on recovery of GI function
  - Time to recovery of GI function (GI-2)
  - Time to discharge order written, appetite and nausea assessment and vomiting episodes
- Additional endpoints
  - Nasogastric tube insertion, length of hospital stay, time to passage of first flatus, time to bowel sounds

Clinical Effectiveness – POI (3)

- Results (Beck et al. 2014 cont.)
  - Median time to first tolerated meal from 1st dose was 25.3 hours in the ipamorelin group vs 32.6 hours in the placebo group (p = 0.15)
  - No differences between study groups for secondary and additional endpoints
  - Subgroup analysis stratified by surgery type
    - Ipamorelin showed shorter bowel recovery times in subjects undergoing open laparotomy

- A review article (Ishida et al. 2020) commented: "In patients undergoing bowel resection, ipamorelin did not shorten the time to first meal intake compared with placebo. This phase II clinical trial did not show any significant difference in measurable colonic functions between ipamorelin and placebo. Due to these disappointing results, its development was discontinued. "

Clinical Effectiveness – POI (4)

Conclusion

- FDA has not identified data to support the effectiveness of ipamorelin in treatment of POI
- There is currently an FDA-approved drug with established efficacy for the management of postoperative ileus following bowel resection surgery

Nonclinical Safety

- Nonclinical acute toxicity, repeat-does toxicity, genotoxicity, or carcinogenicity studies were not found in the scientific literature

- In rodents, ghrelin receptor activation in brain regions that process reward stimulates a dopamine surge (a typical pharmacological response induced by drugs of abuse) and increases heroin consumption and seeking activity (Maric et al. 2012)
  - Nonclinical studies are lacking to demonstrate whether ipamorelin has reinforcing and addictive properties

- Developmental and Reproductive Toxicity
  - Systemic administration of ghrelin to mice during fertilization, early embryonic development, and implantation periods: (i) delayed embryo development, (ii) increased percentage of atrophied fetuses, and (iii) reduced fetal and maternal weight gain (Luque et al. 2014)
  - It remains to be determined whether ipamorelin (free base) and ipamorelin acetate, substances that like ghrelin act as a ghrelin receptor agonists, can negatively impact fertilization and embryofetal development as ghrelin did in the study cited above

Nonclinical Safety - Conclusion

- Acting as a ghrelin receptor agonist, ipamorelin-related substances may have behavioral reinforcing properties, which can contribute to development of addiction, and may negatively affect reproductive health and pregnancy outcomes

- Nonclinical toxicity studies were too limited in scope and duration to inform safety considerations for potential clinical uses of ipamorelin-related substances

Clinical Safety (1)

- FDA Adverse Event Reporting System (FAERS)
  - 2 reports of non-serious adverse events (AE) associated with compounded products
    - Increased lacrimation and headache after using nasal spray containing single ingredient ipamorelin
    - Arthralgia with left elbow joint pain after using injectable product containing ipamorelin and sermorelin
  - Our ability to interpret AE reports from FAERS is limited by factors such as insufficient case details and concomitant medications

Clinical Safety (2)

- Beck et al. 2014:
  - AEs reported were mild to moderate in severity and were generally related to surgery or underlying disease
  - Most common AEs:
    - Nausea, vomiting and abdominal distention (comparable between ipamorelin and placebo)
    - Hypokalemia (12.5% ipamorelin vs 3.4% placebo)
    - Insomnia (10.7% ipamorelin vs 5.2% placebo)
    - Hyperglycemia at discharge (14.3% ipamorelin vs 8.6% placebo)
  - Serious Adverse Events (SAEs)
    - Infection (10.7% ipamorelin vs 10.3% placebo)
    - Anastomotic leak (3.6% ipamorelin vs 1.7% placebo)
    - Readmission (12.5% ipamorelin vs 8.6% placebo)
    - Death (2 ipamorelin vs 0 placebo)

Additional safety information on IGF-1

- Increased IGF-1 and safety:
  - There are known potential risks associated with elevated GH and IGF-1 levels
  - Warnings and precautions are included in FDA-approved recombinant human GH (rhGH) labeling including increased risk of neoplasm, glucose intolerance and diabetes mellitus, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis in pediatric patients, progression of preexisting scoliosis in pediatric patients, and pancreatitis
  - There are insufficient data to conclude that ipamorelin-related substances would not raise safety concerns similar to those associated with approved products that stimulate GH release

Additional safety information – Immunogenicity Concerns

- Ipamorelin-related substances are 5 amino acid peptides
- Peptides may elicit an immune response; this response may be enhanced when peptides are given via the SC ROA
- Ipamorelin-related substances pose a risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
  - The nomination did not include, and FDA is not aware of, information about ipamorelin-related substances to suggest that the substances do not present these risks

Clinical Safety – Conclusion (1)

- No clinical safety data for ipamorelin administered by SC ROA
- Although it is unclear whether the deaths reported in the POI study were related to ipamorelin, their occurrence in ipamorelin-treated subjects, along with the higher rates of hypokalemia and hyperglycemia, raises safety concerns about the use of ipamorelin in compounding
- There are known potential risks associated with the use of drug products that increase IGF-1 levels, such as glucose intolerance and fluid retention. There are insufficient data to conclude that ipamorelin-related substances would not present safety concerns similar to those associated with approved growth hormone products

Clinical Safety – Conclusion (2)

- Although ipamorelin-related substances are peptides containing only 5 amino acids, FDA is concerned about potential risk of immunogenicity when given SC due to potential for aggregation and peptide-related impurities

- There are currently available FDA-approved drugs for the: diagnosis of GHD in children and adults, treatment of GHD in adults, and treatment of short stature in children. There is an FDA-approved product for the management of postoperative ileus

Evaluation Summary

- On balance, physiochemical characterization, information on historical use, evidence of effectiveness, and safety information identified for both ipamorelin (free base) and ipamorelin acetate weigh against their being added to the 503A Bulks List
  - Ipamorelin (free base) and ipamorelin acetate are not well characterized from a physicochemical perspective, due in part to lack of impurity and endotoxin testing
  - Although there is some evidence of compounded ipamorelin's use in humans, there is lack of nonclinical and clinical safety data and lack of clinical effectiveness data for ipamorelin-related bulk drug substances delivered via the SC route for GHD or POI
  - Potential serious safety risks associated ipamorelin related bulk drug substances
  - These are particularly concerning given the existence of drugs approved by FDA for GHD and POI, which are serious conditions.

Recommendation

- After considering the information currently available, a balancing of the four evaluation criteria weighs **against** ipamorelin-related bulk drug substances (ipamorelin (free base) and ipamorelin acetate) being added to the 503A Bulks List


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Kisspeptin-10

Pharmacy Compounding Advisory Committee Meeting

October 29, 2024

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Special Thanks to: **Office of New Drugs Division of Urology - Obstetrics and Gynecology (DUOG)**

Nomination

- Kisspeptin-10 was nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
- Kisspeptin-10 was evaluated for the treatment of secondary hypogonadism in men
- Products proposed in the nomination are: 1 mg/mL solutions for injection for subcutaneous (SC) and intramuscular (IM) administration

Evaluation Criteria

- Physical and chemical characterization
- Safety
- Historical use in compounding
- Available evidence of effectiveness or lack of effectiveness

Physical and Chemical Characterization (1)

Kisspeptin-10:

- Synthetic peptide containing 10 amino acids
- Can be synthesized through solid-phase peptide synthesis process
- Water solubility is 2.0 mg/mL

Stability:

- Reportedly stable as a powder for one year under -20°C storage conditions
- Peptides such as kisspeptin-10 can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, temperature, concentration, in-process related impurities, excipients etc.), which may lead to the **aggregation and degradation** of peptides

Physical and Chemical Characterization (2)

Likely impurities:

- Peptide-related impurities, peptide synthesis process-related impurities, and starting materials
  - Solid phase synthesis may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions
- In the nominator provided certificate of analysis (CoA), the total impurities are not more than (NMT) 2.0%, and largest single impurity is NMT 1.0%
- However, information is lacking about the nature and control of individual peptide-related impurities, including aggregates, and variants

Physical and Chemical Characterization - Conclusion

- Not well characterized from the physical and chemical characterization perspective
  - Certain critical characterization data such as likely impurities (peptide-related impurities, including aggregates, and variants) were neither found in the publicly available scientific literature nor were provided in the CoA
- Concern about the potential for immunogenicity when formulated as injectable dosage forms for SC and IM administration due to the longer amino acid chain and potential peptide-related impurities as well as potential aggregates

Nonclinical - Safety (1)

Acute toxicity:

- In vitro: High concentrations of kisspeptin-10 triggered pro-atherosclerotic effects in cultured endothelial cells and arterial smooth muscle cells (e.g., increased expression of inflammatory markers; adhesion of monocytes to endothelial cells) (Sato et al. 2017)

Repeat dose toxicity:

- The IV no-observed adverse effect level (NOAEL) in dogs was 1 mg/kg after 14 days of daily treatment (Terse et al. 2021)
- Kisspeptin-10 (5 or 12.5 µg/kg/h, SC infusion, 4 weeks) accelerated development of aortic atherosclerotic lesions and vascular inflammation in atherosclerosis-prone ApoE$^{-/-}$ mice (Sato et al. 2017)

Nonclinical - Safety (2)

FDA did not identify nonclinical genotoxicity, developmental and reproductive toxicity, or carcinogenicity studies with kisspeptin-10

Conclusion:

- Although the pro-atherosclerotic effects of kisspeptin-10 are concerning, their clinical relevance remains unclear
- Nonclinical toxicity studies available at the time of this evaluation were too limited in scope and duration to inform safety considerations for potential clinical uses of kisspeptin-10

Clinical Safety - FDA Adverse Event Reporting System (FAERS)

- Retrieved *one* adverse event (AE) report from a 17-year-old male with hypogonadotropic hypogonadism treated with compounded kisspeptin-10
  - Subject gained weight and his estrone increased (specific numbers not provided)
  - Interpretation of the case is limited by an unclear temporal relationship and insufficient information

Clinical Safety - Immunogenicity Concerns

- Kisspeptin-10 is a 10 amino acid peptide
- Peptides may elicit an immunogenic response; this response may be enhanced when peptides are given via the SC route of administration (ROA)
- Kisspeptin-10 given via the SC ROA may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
  - The nomination did not include, and FDA is not aware of, information about kisspeptin-10 to suggest that this substance does not present these risks

Clinical Safety - Clinical Studies

- Kisspeptin-10 has been administered via the:
  - IV ROA in several small studies
  - SC ROA in a single study in 35 healthy women
  - No studies administered kisspeptin-10 via the IM ROA
- Most studies did not include information on safety; no serious AEs were reported
- Studies were of short duration and had small sample sizes
- No published clinical trials that assessed the safety of kisspeptin-10 when administered chronically or on a fixed schedule for over one day

Clinical Safety - Conclusion

- Based on available data, there is a lack of information about whether kisspeptin-10 can be safely used in the intended population, the appropriate dose range, and frequency and duration of dosing for the proposed routes of administration

- As a peptide with 10 amino acids that is administered through the SC and IM ROA, kisspeptin-10 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities

Historical Use in Compounding (1)

- Kisspeptin-10 was first described in 2004
  - Insufficient information how long it has been used in pharmacy compounding
- Studied for its effects on gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) in the reproductive system
  - Unclear whether the kisspeptin-10 products used in these studies were compounded

Historical Use in Compounding (2)

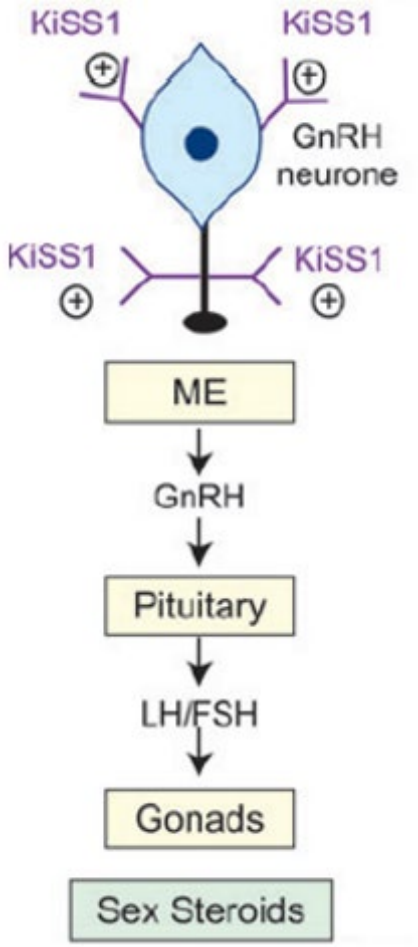
- FAERS case report indicated that a compounded injectable (SC ROA) kisspeptin-10 product was being used for hypogonadotropic hypogonadism
- Kisspeptin-10 is promoted online:
  - For weight loss and fertility on several clinics' websites
  - One website referred to kisspeptin-10 as an "alternative" to human chorionic gonadotropin (HCG)
  - As injectable and troche formulations
- Kisspeptin-10 is not a component of an approved product in any country, nor is it found in the European or Japanese Pharmacopeias

Pharmacology

Kisspeptin-10:

- Endogenous and synthetic forms of kisspeptin-10 bind to and activate the G-protein coupled receptor GPR-54 (KISS1R)
  - GPR-54 activation in GnRH-expressing hypothalamic neurons results in the increase of pituitary secretion of gonadotropins, which, in turn, can increase secretion of sex hormones from the gonads
- The frequency of administration of kisspeptin-10 impacts the pharmacological outcome
  - In nonclinical studies, tachyphylaxis (i.e., a rapid progressive loss of effect) develops when kisspeptin-10 is delivered uninterruptedly for a long period to animals

GnRH: The **pulsatile** secretion of GnRH initiates puberty and maintains overall reproductive function



Kisspeptin-GnRH Pathway
(Adapted from Skorupskaite et al. 2014)
Abbreviations: KiSS1 = kisspeptin, ME = median eminence, FSH = follicle stimulating hormone, LH = luteininzing hormone

Proposed Use and Dosage Forms

- Kisspeptin-10 was evaluated for the treatment of secondary hypogonadism in men
- Products proposed in the nomination are: 1 mg/mL solutions for SC and IM administration

Pharmacokinetics (PK)

Nonclinical:

- In rats that received an IV injection of kisspeptin-10 (1 mg/kg), the half-life of the peptide was found to be extremely short (<1 min) (Liu et al. 2013)
- The nonclinical PK profiles of kisspeptin-10 delivered via the nominated ROAs (SC and IM) are unknown at this time

Clinical:

- In healthy men that received an IV infusion of kisspeptin-10, the half-life was 3.8 (±0.3) minutes (Jayasena et al. 2011)
- After SC administration, the peak levels (Cmax) were lower after SC administration compared with IV administration in healthy women; authors did not report the absolute SC bioavailability of kisspeptin-10 (Jayasena et al. 2011)

Overview of Hypogonadism

- Clinical syndrome that results from failure of testis to produce physiological concentrations of testosterone and/or a normal number of spermatozoa due to pathology in the Hypothalamic-Pituitary-Gonadal (HPG) axis
- Classified as primary or secondary:
  - Primary: dysfunction arising from the level of the testes
    - Low testosterone, elevated gonadotropins (LH and FSH) (hypergonadotropic hypogonadism)
  - Secondary: dysfunction arising from the level of the hypothalamus or pituitary
    - Low testosterone, low or inappropriately normal LH and FSH (hypogonadotropic hypogonadism, HH)

Idiopathic Hypogonadotropic Hypogonadism (IHH)

- Results from the failure of normal episodic GnRH secretions, leading to delayed puberty and infertility

- Previously thought to be a permanent condition, but it now known that a subset of patients with IHH spontaneously recover function of their reproductive axis – “reversal” – not always long-lasting

Treatment of Secondary Hypogonadism

- Treatment depends in part on underlying etiology and patient's goals for immediate fertility
- Products approved for treatment of secondary hypogonadism:
  - Testosterone products
  - Human Chorionic Gonadotropin (HCG)
  - Follicle Stimulating Hormone (FSH)
- Testosterone can impair spermatogenesis and is not recommended in males interested in current or future fertility
- In men with IHH, spermatogenesis can be initiated with exogenous gonadotropins (e.g., HCG)

Clinical Effectiveness - Clinical Studies (1)

- Four published studies using kisspeptin-10 in subjects (men and women) with IHH (Young et al. 2013; Chan et al. 2014; Lippincott et al. 2016; Lippincott et al. 2018)
  - Some of the studies included subjects who had IHH with reversal
- Kisspeptin-10 was administered as an IV bolus or IV infusion
  - None of the studies administered kisspeptin-10 intermittently over a prolonged period
- Measured LH, FSH, testosterone (T), and estradiol (E2)
- Study objectives were not to treat subjects with IHH; rather investigators aimed to probe the kisspeptin/GnRH pathway in this population
- Results from these studies are mixed, but generally there was no LH response after exogenous kisspeptin-10 administration in non-reversed IHH subjects

Preservation of Spermatogenesis with Testosterone Therapies

- Nominated for “Hormonal therapy to include treatment of male hypogonadism, preservation of spermatogenesis with testosterone therapies”
- Evaluated “preservation of spermatogenesis with testosterone therapies” in the context of the treatment of secondary hypogonadism in men
- We identified a single study that administered kisspeptin-10 as an IV bolus to 6 men with IHH on their prescribed clinical sex steroid treatment of exogenous T (Lippincott et al. 2018)
  - No participant responded to kisspeptin-10 with an LH response, and sperm concentrations or pregnancies were not measured as an endpoint in this small study

Clinical Effectiveness - Clinical Studies (2)

George et al. 2013:

- Proof-of-concept study in 5 men with type 2 diabetes and low T levels and 7 age-matched healthy men
  - None of the men had hypogonadism symptoms at recruitment
- IV bolus study: 100 µg GnRH at the first visit and 0.3 µg/kg kisspeptin-10 at the second visit
  - T not measured; per authors, "transient rises in LH response to acute kisspeptin administration are not associated with sustained increases in testosterone"
  - LH increased in both groups of men after kisspeptin-10 administration; greater LH stimulation after GnRH administration
- IV infusion study: No treatment at first visit and IV infusion of kisspeptin-10 (4 µg/kg/h) for 11 hours at second visit
  - Mean LH, LH pulse frequency, and total T increased (from 245.1 ± 28.8 ng/dL to 328.8 ± 30 ng/dL) after kisspeptin-10 infusion

Clinical Effectiveness - Conclusion

- Insufficient evidence to make a conclusion on the effectiveness of kisspeptin-10 as a treatment option for men with secondary hypogonadism
- It is not possible to draw any meaningful conclusions on effectiveness from these studies due to the small number of subjects included, the exploratory nature of the studies, and the dosing of kisspeptin-10 (ROA and frequency of administration) used in the studies
- We are not aware of studies that administered kisspeptin-10 via the proposed routes of administration (IM or SC) in men with hypogonadism
- Unclear if chronic IV administration of kisspeptin-10 would confer any clinical benefit in this patient population
- There are several FDA-approved treatments that are indicated to treat secondary hypogonadism in men

Evaluation Summary

On balance, the physicochemical characterization, information on historical use, evidence of effectiveness, and safety information identified for kisspeptin-10 weigh **against** inclusion of this substance on the 503A Bulks List.

In particular, FDA's proposal regarding this substance is based on the fact that kisspeptin-10:

- Is not well characterized from a physicochemical perspective;
- Lack of information about whether kisspeptin-10 can be safely used in the intended population and on immunogenicity risks;
- Insufficient evidence to make a conclusion on the effectiveness of kisspeptin-10 as a treatment option for men with secondary hypogonadism, and there are FDA-approved drug products that are indicated to treat secondary hypogonadism, a potentially serious condition.

Recommendation

After considering the information currently available, a balancing of the four evaluation criteria weighs **against** kisspeptin-10 being added to the 503A Bulks List.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Process for Identifying Drugs for the Withdrawn or Removed List

Pharmacy Compounding Advisory Committee Meeting

October 29, 2024

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Statutory Framework

- One of the conditions that must be satisfied for a drug product to qualify for the exemptions under sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) is that the compounder does not compound a drug product that appears on a list published by the Secretary of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (Withdrawn or Removed List), codified at § 216.24.
- A drug product that is included in the Withdrawn or Removed List is not eligible for the exemptions provided in sections 503A or 503B.
- FDA has reviewed and added 85 bulk drug substances to the Withdrawn or Removed List to date.

Process for Developing the Withdrawn or Removed List

- FDA periodically reviews available information on drugs withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective with the goal of identifying possible new entries for the list.
- The information reviewed may include:
  - *Federal Register* notices announcing withdrawal of approval of a new drug application (NDA) or abbreviated new drug application (ANDA) for safety or effectiveness reasons
  - *Federal Register* notices announcing an Agency determination that a drug product that was voluntarily withdrawn from sale was withdrawn for reasons of safety or effectiveness

Process for Developing the Withdrawn or Removed List

- FDA also reviews available information to determine whether any approvals of new drug applications would warrant modifications to existing entries on the list
- Appropriate divisions within the Office of New Drugs (OND) evaluate each identified candidate or proposed modification using the available information about the drug.
- The responsible division will prepare a review of the information that documents its recommendations as to whether to include the drug on the withdrawn or removed list, or remove a drug from the list, or modify an entry.

Process for Updating the Withdrawn or Removed List

FDA will update the Withdrawn or Removed List through notice and comment rulemaking (as stated in a final rule published in October 2016).

- FDA intends to propose regulations to revise the list when we identify drugs that we tentatively determine should be listed.
- FDA also intends to propose regulations when we tentatively determine that changes to the status of drug products already on the list should result in a revision to their listing.
- Generally, FDA will finalize any additions or modifications to the list after consulting the Advisory Committee about the relevant drug, and after providing an opportunity for public comments to be submitted on a proposed rule.

Current Drug Identified for the Withdrawn or Removed List

FDA is considering including on the list:

Hydroxyprogesterone caproate: All drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous birth.

Hydroxyprogesterone Caproate for Withdrawn or Removed List

Pharmacy Compounding Advisory Committee Meeting
October 29, 2024

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Overview of Withdrawn or Removed List

- The Withdrawn or Removed List (21 CFR 216.24)[1]
  - Under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, FDA has established a list of drug products that were withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective
- Drug products on the withdrawn or removed list may not be compounded under the exemptions provided by sections 503A or 503B

[1] CFR = Code of Federal Regulations

MAKENA Regulatory History (1)

- February 3, 2011: FDA approved MAKENA (hydroxyprogesterone caproate) injection 250 mg/mL (New Drug Application (NDA) 021945)
  - Indicated to reduce the risk of preterm birth (PTB) in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (sPTB)
  - FDA approved MAKENA based on evidence from Trial 002 which demonstrated an effect on gestational age of delivery < 37 weeks (gestational age is an intermediate clinical endpoint)[2]

[2] An intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality that, in the context of accelerated approval, is considered reasonably likely to predict the drug's effect on irreversible morbidity or mortality or other clinical benefit

MAKENA Regulatory History (2)

- MAKENA approval (continued)
  - Approved under the accelerated approval pathway (21 CFR 314 subpart H)[3]
  - Sponsor was required to conduct postmarketing confirmatory trial to verify and describe MAKENA's clinical benefit
- Sponsor conducted postmarketing confirmatory study, Trial 003, which evaluated the effect of MAKENA gestational delivery <35 weeks and neonatal morbidity/mortality
  - Failed to verify the predicted clinical benefit of MAKENA to the neonate and did not even show an effect on gestational age (<37 weeks) that was the basis of the accelerated approval

[3] FDA approves a drug based on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict the drug's clinical benefit, rather than based on a direct measurement of clinical benefit or on a surrogate endpoint that is validated (i.e., known) to predict clinical benefit. Sponsors of drugs approved under the accelerated approval pathway have been required to conduct a postmarket confirmatory trial designed to verify the predicted clinical benefit.

MAKENA Regulatory History (3)

- October 5, 2020: FDA proposed withdrawing approval of MAKENA
  - The available evidence post-approval demonstrated that MAKENA was no longer shown to be effective under its approved conditions of use
  - Sponsor requested a hearing

MAKENA Regulatory History (4)

- October 17 to 19, 2022: Hearing
  - All members of the ORUDAC,[4] which was present at the hearing, voted to advise FDA that Trial 003 did not verify the clinical benefit of MAKENA on neonatal morbidity and mortality from complications of preterm birth
  - Almost all members voted to advise FDA that available evidence does not demonstrate that MAKENA is effective for its approved indication
  - The committee recommended FDA should not allow MAKENA to remain on the market while another confirmatory study is designed and conducted

[4] ORUDAC - Obstetrics, Reproductive and Urologic Drugs Advisory Committee

MAKENA Regulatory History (5)

- January 19, 2023: FDA Presiding Officer's Report stated that she did "not think there is a favorable benefit-risk profile to support MAKENA's remaining on the market and recommend[ed] approval be withdrawn"

- April 6, 2023: The FDA Commissioner and Chief Scientist issued a decision withdrawing the approval of MAKENA and the Abbreviated NDAs (ANDAs) that referenced MAKENA

- May 15, 2023: FDA published a notice in the Federal Register announcing the availability of the final decision to withdraw the approval of MAKENA

Withdrawal of Hydroxyprogesterone Caproate Products

- FDA's determination about the unfavorable benefit-risk profile was specific to the conditions of use for which MAKENA had been approved; therefore, the withdrawal of approval was specific to MAKENA and the generics that referenced MAKENA, which were indicated to reduce the risk of PTB in women with a singleton pregnancy who have a history of sPTB

- Withdrawal of approval of MAKENA does not affect the approval status of drug products containing hydroxyprogesterone caproate that are currently approved for different indications; these indications are in non-pregnant women:
  - Treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV)
  - Management of amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology
  - As a test for endogenous estrogen production and for the production of secretory endometrium and desquamation

Recommendation

FDA recommends the following entry be added to the Withdrawn or Removed List:

Hydroxyprogesterone caproate: All drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.


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